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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,092	06/18/1999	MICHAEL TEWES	TEWESETAL	2371
25889	7590	10/18/2004	EXAMINER	
WILLIAM COLLARD COLLARD & ROE, P.C. 1077 NORTHERN BOULEVARD ROSLYN, NY 11576			LEE, SHUN K	
			ART UNIT	PAPER NUMBER
			2878	

DATE MAILED: 10/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/319,092	TEWES ET AL.
Examiner	Art Unit	
Shun Lee	2878	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 30 September 2004.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 22-25,28,31,32,35-40 and 42-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 22-25,28,31,32,35-40 and 42-49 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 06 December 2002 and 15 August 2003 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 September 2004 has been entered.

Claim Objections

2. Claim 22 is objected to because of the following informalities: "for focusing the beam between said first and said at least a second dichroic beam splitter" on lines 21-22 in claim 22 should probably be --at which the focus of the beam is located-- (since the pinhole array is not for focusing the beam between said first and said at least a second dichroic beam splitter). Appropriate correction is required.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

Art Unit: 2878

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688) and Qian *et al.* (Applied Optics 30:1185-1195, April 1991).

In regard to claims **22-24**, Jacobsen discloses (Figs. 1-3) an apparatus comprising:

- (a) a support body (21, 31);
- (b) a pinhole array (8) comprising at least one pinhole (8) coupled to said support body (21, 31);
- (c) at least one detector (11) coupled to said support body (21, 31);
- (d) a lens array (10) comprising at least one lens (10), coupled to said support body (21, 31), and positioned between at least one pinhole (8) in said pinhole array (8) and said at least one detector (18), said lens array (10) for focusing an emission light passing through said at least one pinhole (8) and onto said at least one detector (11); and
- (e) a plurality of dichroic beam splitters comprising a first dichroic beam splitter (7) and at least a second dichroic beam splitter (9) coupled to said support body (21, 31) in a beam path and wherein at least one pinhole (8) from said pinhole array (8)

is disposed between said first dichroic beam splitter (7) and said at least a second dichroic beam splitter (9) for focusing the beam between said first (7) and said at least a second (9) dichroic beam splitters.

While Jacobsen also discloses (column 4, lines 32-47) that the apparatus comprises a commercial confocal laser scanning microscope (CLSM) wherein the stimulating light is supplied by a laser (1), the apparatus of Jacobsen lacks an explicit description of a fiber optic waveguide disposed within a coupling connection coupled to the support body for coupling in a stimulating light and that the support is a fluorescence correlation spectroscopy module arrayed in an optical inlet and outlet of a microscope. However, commercially available confocal laser scanning microscopes are well known in the art. For example, Engelhart *et al.* teach (column 1, lines 34-42; Fig.) to couple a laser (1) to a microscope via an optical module (8) having an optical fiber (4) to isolate the laser (1) from the microscope. Qian *et al.* teach (second paragraph on pg. 1186) it is known in the art that "Most FCS and FPR experiments are carried out on a standard epifluorescence microscope which is coupled to a laser in a confocal geometry". Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a fiber optic waveguide coupling connection coupled to the support body for mounting to the optical inlet and outlet of the commercially available microscope in the apparatus of Jacobsen, in order to couple elements (such as the laser which provides the stimulating light) to the microscope while isolating the elements from the microscope and that the apparatus of Jacobsen is useful for obtaining

Art Unit: 2878

fluorescence data in well known fluorescence experiments such as FCS (*i.e.*, fluorescence correlation spectroscopy).

6. Claims 25 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688) and Qian *et al.* (Applied Optics 30:1185-1195, April 1991) as applied to claim 22 above, and further in view of Chande (US 4,844,574).

In regard to claim 25 which is dependent on claim 22, the modified apparatus of Jacobsen lacks a collimator for generating a parallel light beam that is disposed within said support body in an excitation beam path after said coupling connection. Chande teaches (column 3, lines 19-25; Fig. 1) to provide a collimator (108) in order to intercept the fiber emitted beam (column 3, lines 19-25). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a collimator in the modified apparatus of Jacobsen, in order to intercept and collect the fiber emitted beam as taught by Chande.

In regard to claim 39 which is dependent on claim 22, the modified apparatus of Jacobsen lacks a collimator is tuned to the numerical aperture of the fiber optical waveguide. Chande teaches that the focal length (f_1) and clear aperture (*i.e.*, parallel light beam diameter D_1) of the collimator (108) must be selected in order to intercept the fiber-emitted beam (column 3, lines 19-25). It is noted that the numerical aperture is defined as the sine of half the acceptance angle (*i.e.*, see θ_{EM} in Fig. 1 of Chande). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to match the focal length and clear aperture (*i.e.*, numerical aperture) of

the collimator to the emitted beam angle (*i.e.*, numerical aperture) of the fiber in the modified apparatus of Jacobsen, in order to intercept and collect the fiber emitted beam as taught by Chande.

7. Claims 28, 31, 32, 35, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688) and Qian *et al.* (Applied Optics 30:1185-1195, April 1991) as applied to claim 22 above, and further in view of Schalz (US 5,585,964) and Jörgens (US 5,535,052).

In regard to claim 28 which is dependent on claim 22, the modified apparatus of Jacobsen lacks a filter array (*e.g.*, at least two frequency selective filter devices) and the beam splitter are set on a receptacle holder removably inserted within the support body. Schalz teaches that holding elements (*i.e.*, sliders, carriers, or slide-in-modules; see column 2, lines 36-54) have “ ... corresponding precision-stop-surfaces ... for the exact positioning of the holding element ... ” (see also column 4, lines 21-23) and that these holding elements are designed to contain optical elements such as fluorescence-dividing cubes with switching positions (column 2, lines 60-67). Jörgens teaches (column 5, lines 47-53) that filter, beam splitters, and/or mirrors are used to provide a plurality of confocal detection channels. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide beam splitters with associated filters in a removably inserted common receptacle holder (*i.e.*, sliding mechanism) in the modified apparatus of Jacobsen, in order to select particular

Art Unit: 2878

combinations of beam splitter with associated filters so as to obtain a desired range of wavelengths in each of a plurality of confocal detection channels.

In regard to claims **31** and **32** which are dependent on claim 28, the modified apparatus of Jacobsen lacks at least one mirror. Jörgens teaches (column 5, lines 47-53) that filter, beam splitters, and/or mirrors are used to provide a plurality of confocal detection channels. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide at least one mirror in the modified apparatus of Jacobsen, in order to obtain a plurality of confocal detection channels.

In regard to claim **35** which is dependent on claim 28, the modified apparatus of Jacobsen lacks a detailed description of the receptacle holder (*i.e.*, slider), characterized in that the support body (4) for receiving the receptacle holder (15) is provided with shaped surfaces (25), to which the receptacle holder (15) provided with complementarily shaped surfaces arrayed on the support body in the beam path can be fixed. Schalz teaches that holding elements (*i.e.*, sliders, carriers, or slide-in-modules; see column 2, lines 36-54) have “... corresponding precision-stop-surfaces ... for the exact positioning of the holding element ...” (see also column 4, lines 21-23) and that these holding elements are designed to contain optical elements such as fluorescence-dividing cubes with switching positions (column 2, lines 60-67). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide corresponding precision-stop-surfaces in the sliders of the modified apparatus of Jacobsen, in order to have exact positioning and alignment of the optical elements in the sliders as taught by Schalz.

In regard to claim 37 which is dependent on claim 28, the modified apparatus of Jacobsen lacks that the support body is made with cavities for receiving the receptacle holder, wherein the said cavities have suitable lateral surfaces designed to accommodate the oriented reception of the receptacle holder. Schalz teaches that a carrier (*i.e.*, receptacle holder) has corresponding precision-stop-surfaces (*e.g.*, lateral surfaces of a cavity) for exact positioning (column 2, lines 46-59) without additional alignment or optical adjustment (column 6, lines 29-40). Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide cavities with corresponding precision-stop-surfaces in the modified apparatus of Jacobsen, in order to have exact positioning without additional alignment or optical adjustment as taught by Schalz.

In regard to claim 38 which is dependent on claim 37, Schalz and Jörgens is applied as in claims 28, 31, 32, and 35 above.

8. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688) and Qian *et al.* (Applied Optics 30:1185-1195, April 1991) as applied to claim 22 above, and further in view of Schalz (US 5,585,964).

In regard to claim 36 which is dependent on claim 22, the modified apparatus of Jacobsen lacks an explicit description of a connection flange for attaching the support body to the connection of the microscope and a support body which is made in one piece from a metallic material. Schalz teaches (column 4, lines 1-25) that modularly designed microscopes should be manufactured of metal such as aluminum or brass in a

one-piece construction-type in order to increase rigidity. Schalz also teaches (column 6, lines 29-40) that a modular microscope system makes it possible to attach modules (*i.e.*, support body) via precision attachment surfaces (*e.g.*, connection flange) without additional alignment or optical adjustment. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to manufacture the modules in the modified apparatus of Jacobsen as a metallic one-piece construction-type that can be attached to a precision attachment surface of a modular microscope, in order to have rigid module that can be attached to a microscope without additional alignment or optical adjustment as taught by Schalz.

9. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), and Chande (US 4,844,574) as applied to claim 39 above, and further in view of Schalz (US 5,585,964) and Jörgens (US 5,535,052).

In regard to claim 40 which is dependent on claim 39, Schalz and Jörgens is applied as in claims 28, 31, 32, 35, 37, and 38 above.

10. Claims 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen (US 5,329,352) in view of Engelhart *et al.* (WO 96/06377 with corresponding US 5,903,688), Qian *et al.* (Applied Optics 30:1185-1195, April 1991), Schalz (US 5,585,964), and Jörgens (US 5,535,052).

In regard to claim 42, Jacobsen in view of Engelhart *et al.* and Qian *et al.* is applied as in claims 22-24 above. Schalz and Jörgens is applied as in claims 28, 31,

Art Unit: 2878

32, 35, 37, and 38 above. Jacobsen also discloses (Figs. 1-3) that the beams passes through or reflect from the plurality of beamsplitters (7, 9).

In regard to claim 43, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claim 42 above. The apparatus of Jacobsen lacks that each of the optical components and said at least one mirror can be removed from the support body and inserted in a different order in a different one of said plurality of cavities or rotated 180° and reinserted. Schalz teaches (column 5, lines 8-20) a fluorescence-divider turret (31 in Figs 1a and 1b) inserted as a slide in module. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a fluorescence-divider turret in the apparatus of Jacobsen, in order to select a particular combination of beam splitter with associated filters (*i.e.*, a particular fluorescence-divider) by sliding in the (*e.g.*, 180°) rotated fluorescence-divider turret module so as to obtain a desired range of wavelengths in the confocal detection channel.

In regard to claim 46, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claim 42 above. Jacobsen also discloses (Figs. 1-3) that the focal point of said emission light is after said beam splitter (7) and a focal point of said stimulation light is before said beam splitter (7).

In regard to claim 47, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claim 42 above. Jacobsen also discloses (Figs. 1-3) that a focal point of said stimulation light is before said beam splitter (7).

In regard to claims 44, 45, 48, and 49, Jacobsen in view of Schalz, Engelhart *et al.*, Qian *et al.*, and Jörgens is applied as in claims 46 and 47 above.

Response to Arguments

11. Applicant's arguments filed 30 September 2004 have been fully considered but they are not persuasive.

Applicant argues (first paragraph on pg. 17 of remarks filed 30 September 2004) that there is no suggestion to combine the references of Jacobsen, Engelhart *et al.*, and Qian *et al.* since these microscopes are all designed entirely different from each other and no person skilled in the art would replace the photoelectric detector (11) in Jacobsen, with a time depending detector as required for fluorescence correlation spectroscopy. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is important to recognize that fluorescence correlation spectroscopy comprises data analysis of time resolved fluorescence spectroscopy data (see e.g., Qian *et al.*). It should also be noted that the microscope of Engelhart *et al.* is a confocal laser scanning microscope (abstract) and the microscope of Qian *et al.* is a modified confocal laser scanning microscope ("Although the system just described and the standard scanning

confocal fluorescence microscope are similar overall,^{11,12} they differ in certain respects. Scanning is not required in conventional FCS or FPR, although it can be useful in specific situations.¹³⁻¹⁵; last paragraph in left column on pg. 1187). In addition, Jacobsen states (column 2, line 47 to column 3, line 17) that "As a confocal scanning light microscope, all arrangements are suitable in which the sample piece is scanned by a focusing light beam and in which a portion of the transmitted or scattered light is imaged by an imaging optical beam path onto an aperture or onto a system of apertures and in which the portion of said light passing through the aperture is measured by a photoelectric detector and, with the aid of said measuring signal, an image of the entire sample piece is produced. ... The spectroscopic measuring processes may be any methods which are based on recording the wavelength-dependent intensity of visible light or of light having a wavelength in the vicinity of visible light, e.g. of 100 nm to 20 µm. Methods to be cited in particular are absorption spectroscopy in the ultraviolet, visible, near-infrared and infrared region as well as fluorescence and Raman spectroscopy. ... As a simultaneously recording spectrometer, all arrangements may be cited which allow, for the entire wavelength range applicable to the spectroscopic process in question or for parts thereof, time resolution measurement of the radiant intensity contained in the measuring light per wavelength interval" and (column 4, lines 42-47) that "A commercial CLSM 21 is combined with a commercial triple spectrograph 16 in that a portion of the measuring light passing through the measuring aperture is separated from the measuring channel of the CLSM by a beam splitter 9 and introduced by way of the optical fibres 24 into the spectrograph". Thus the microscope of Jacobsen

is a confocal laser scanning microscope and Jacobsen expressly teach time resolved fluorescence spectroscopy measurements with confocal geometry provided by the confocal laser scanning microscope.

Applicant argues (last paragraph on pg. 17 of remarks filed 30 September 2004) that the proposed modification would change the principle of operation of Jacobsen since the proposed modification would no longer be a process for producing and correlating light microscope images and spectroscopic data as state in column 1, lines 6-8 of Jacobsen. Examiner respectfully disagrees. As discussed above, Jacobsen expressly teach time resolved fluorescence spectroscopy measurements with confocal geometry provided by a confocal laser scanning microscope. Therefore, the proposed modification would not change the principle of operation of Jacobsen since Jacobsen is also directed to time resolved fluorescence spectroscopy measurements with the confocal geometry provided by a confocal laser scanning microscope.

Applicant argues (last two paragraphs on pg. 18 of remarks filed 30 September 2004) that the Jacobsen microscope cannot be a fluorescence correlation spectroscopy microscope since it is specialized for correlating light microscope images and spectroscopic data not a standard epifluorescence microscope images with an optical path between the dichroic beam splitter and the detector that is much too long and unstable. These arguments are not persuasive since applicant fails to provide any evidence that the confocal laser scanning microscope of Jacobsen is unstable and cannot perform time resolved fluorescence spectroscopy measurements such as fluorescence correlation spectroscopy.

Applicant argues (second paragraph on pg. 19 of remarks filed 30 September 2004) that Qian *et al.* would require undue experimentation since Qian *et al.* only suggest to couple the microscope to a laser in confocal geometry but does not teach in detail how a standard microscope is to be changed for FCS measurements. Examiner respectfully disagrees. Qian *et al.* provides detail descriptions of FCS measurements in confocal geometry (see e.g., Fig. 1).

Conclusion

12. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 2878

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shun Lee whose telephone number is (571) 272-2439. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Porta can be reached on (571) 272-2444. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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